Remarks

Amendments to the claims

Claims 1-17, 19, and 21-28 are pending. Claim 15 is amended to additionally recite coating the pellets with a rate-controlling membrane that determines drug release. Claims 13 and 21 are amended to clarify the claimed subject matter. Support is found at least in the original claims and at p. 5, lines 9-16; and p. 8, line 16, through p. 11, line 22.

Rejections under 35 U.S.C. § 112

Claims 1-17, 19, and 21-28 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly being overbroad and allegedly lacking enablement. The applicant respectfully disagrees.

The present invention comprises a pellet system. The pellets include inner cores, which inner cores either include, or are coated with, a drug which has particular properties and which is provided in the form of a salt. The inner core is then subsequently coated with a rate-controlling membrane that determines drug release. It is these coated pellets that are subsequently provided with a means adapted to prevent release of drug until the terminal ileum or the colon is reached following oral administration. To state more clearly, the pellet system is a three-component system which includes: (a) an inner core which includes or is coated with drug, (b) a rate-controlling membrane, and (c) a means which is provided to prevent drug release until the colonic region is reached.

The specification contains sufficient description so as to allow a skilled artisan to make and use the compositions defined by claims 1-17, 19 and 21-28. The nature of the active ingredients that may be employed in the compositions of the invention, and how these may be provided, is explained at p. 5, line 28, through p. 7, line 4. What the inner cores may comprise, and how these may be formed as appropriate is discussed at p. 7, lines 6-13. The nature of the rate-controlling membrane is discussed at p. 7, line 15, through p. 8, line 14. How the compositions comprising pellets may, once formed, be thereafter adapted to deliver the drug to the colonic region is described in detail at p. 8, line 16, through p. 11, line 22.

The specification further provides that the cores may contain or be coated with a drug salt (p. 7, lines 6-8) and may optionally comprise sugar spheres (non-pariels) (p. 7, lines 10-13). The drug salt can include any drugs which have (a) a free acid group which can be converted into a salt such as an alkali metal salt or ammonium salt by a simple reaction using for example NaOH or NH_4OH (b) a pKa in the range of 2.0 to 9.0 (p. 5, lines 20-22; p. 6, lines 9-14). One of ordinary skill in the art would know which drug has a free acid group. Further, a simple reference check on documentation in the art such as the Merck Index would indicate the pKa of the free acid group (See for example, the enclosed excerpt). For drug molecules where such documentation is not readily available, one of ordinary skill in the art can readily determine whether the pKa of the free acid group by way of routine technique falls in the range of 2.0 to 9.0. For example, the pKa of carboxylic acid is generally about 4.5. The addition of

electronically withdrawing group such as F or NO_2 would increase the acidity of the carboxylic acid, thus lowering the pKa of the acid. On the other hand, the addition of an electronically donating group such as CH_3 would decrease the acidity of the carboxylic acid, thus increasing the pKa of the acid (see for example, In re Borkowski, 422 F.2d 904, 908 (CCPA, 1970) (holding that the specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation)). Therefore, claims 1, 15, 17, 19 are fully enabled. Moreover, the specification specifically discloses exemplary drugs as ridogrel, other thromboxane synthase A_2 inhibitors and thromboxane A_2/prostaglandin endoperoxide receptor antagonists such as those disclosed in U.S. Patent No. 4,963,573, and sodium cromoglycate (p. 6, lines 3-7). Further, one of ordinary skill in the art may be routinely determine whether a drug is a thromboxane synthase A_2 inhibitor or a thromboxane A_2/prostaglandin endoperoxide receptor antagonist. Therefore, claims 2-3 and 8-12, which are drawn to a specific drug or a specific form of the drug, are fully enabled.

The applicant respectfully points out that much of the Examiner's reasoning for the rejection appears to be implying that the applicant is only entitled to the specific embodiments of the integers of the claimed invention that have been disclosed. As discussed below, although the combination of features (a), (b) and (c) above provides for a novel and non-obvious formulation, each of these individual features may be derived and/or determined routinely by the skilled person. To expect the applicant to limit to exactly the specified embodiments discussed in the

specification would be an unacceptable restriction (see, e.g., In re Fisher, 427 F.2d 833, 839 (CCPA 1970) (holding that the scope of enablement must **only** bear a reasonable correlation to the scope of the claims (emphasis added by the applicant)); see also MPEP § 2164.08).

The specification also teaches that the release rate of the drug is controlled by a water-insoluble but water-permeable coating or coatings formed of polymers (p. 7, lines 15-26). One of ordinary skill in the art would know which polymer is water insoluble but water-permeable or can be made water-permeable (see e.g., Byron, et al., "Effects of heat treatment on the permeability of polyvinyl alcohol films to a hydrophilic solute," in J Pharm Sci. 76(1):65-7 (1987); Alper et al., "Moist wound healing under a vapor permeable membrane.," in J Am Acad Dermatol. 8(3):347-53 (1983); and Lapour et al., "Silicone rubber-hydrogel composites as polymeric biomaterials. VI. Transport properties in the water-swollen state," in Biomaterials 16(8):633-40 (1995)). The specification further defines the term "water permeable to mean that at least 10% of water will penetrate the coating within 2 hours (p. 7, lines 20-24). Exemplary polymers given in the specification include those enumerated at p. 7, line 26, through p. 8, line 7. The rate of release can be further controlled by the thickness of the coating (80 to 300 μm), the nature of the coating (p. 8, line 24, through p. 12, line 5), pH sensitivity for targeting to the colon (p. 9, lines 11-13), and the stability of the coating (stable for 2 to 5 hours for the pellets to reach colon, p. 9, lines 15-18). In addition, the method of controlling the release rate also includes those disclosed in WO 95/35100, which discloses polymers that are broken down or degraded by

colonic bacterial enzymes and starches that are not broken down by the enzymes in the upper gastrointestinal tract but are degraded by enzymes in colon (p. 7, lines 11-12 and 29-30; p. 8, line 1 of WO 95/35100). Therefore, claims 4, 13, 21, and 24-28 are fully enabled.

Claims 1-17, 19 and 21-28 were also rejected under 35 U.S.C. 112, second paragraph, as incomplete for omitting one or more essential elements. The applicant amended claim 15 to moot the rejection of indefiniteness as applied to claims 15-16 and 23 and respectfully traverses the rejection as applied to the rest of the claims.

The pellets described in this application are different from capsules or tablets. One of ordinary skill in the art would readily appreciate the difference between pellets and tablets or capsules. For example, one of ordinary skill in the art would readily recognize that the pellets provided herein may be filled into tablets and/or capsules.

The Examiner's statement that a rate controlling membrane is determined by the type of the coating compound, its pH solubility and thickness is rather confusing. It is the drug releasing rate, not the controlling membrane, which is determined by the type of the coating compound and the pH solubility, thickness, and degradability by enzymes of the compound. A particular type of rate controlling membrane inherently carries with it features or properties such as the type of the compound used, the thickness of the membrane, pH solubility, and degradability by enzymes. Therefore, reciting a rate controlling membrane rather than one of its specific attributes does not render the claims indefinite.

Claim 19 was rejected as indefinite for not reciting an effective amount of the composition for treating the diseases enumerated therein. However, one of ordinary skill in the art would appreciate what amount is effective for treating each of the enumerated diseases (see, for example, Ardizzone, et al., "A practical guide to the management of distal ulcerative colitis," in Drugs 55(4):519-42 (Review) (1998); Prakash, et al., "Oral delayed-release mesalazine: a review of its use in ulcerative colitis and Crohn's disease," in Drugs 57(3):383-408, Review (1999); and Ardizzone, et al., "Guidelines for the treatment of ulcerative colitis in remission," in Eur J Gastroenterol Hepatol. 9(9):836-41, Review (1997)). Therefore, claim 19 is not indefinite for not reciting an effective amount of the composition.

Claims 1-17, 19 and 21-28 were rejected as indefinite for reciting "wherein the composition is adapted to prevent release of the drug until the composition reaches the terminal ileum or the colon following oral administration of the composition." The Examiner alleged that the phrase describes the problem but does not appear to indicate how the problem is to be solved. In light of the foregoing discussion of the rejection under 35 U.S.C. § 112, first paragraph, and the disclosure of the adaptation means provided at p. 8, line 16, through p. 11, line 22, the applicant respectfully submits that the rejection of claims 1-17, 19 and 21-28 as indefinite is moot.

Claim 6 was rejected as indefinite for reciting "EUDRAGIT™ NE30D". EUDRAGIT™ is a trade mark for a polyacrylamide polymer sold by Rohm Pharma. NE30D indicates the specific product used therein bearing the trademark. Therefore, claim 6 is not indefinite.

Claim 13 was rejected as indefinite for reciting the phrase "designed to disintegrate and release the pellets." In light of the amendment to claim 13, the rejection is moot.

Claims 15, 16 and 23 were rejected as indefinite. In light of the amendment to claim 15, the rejection is moot.

Claim 21 was rejected as indefinite for allegedly failing to provided the material with which the tablet is coated. In light of the amendment, the rejection is moot.

Rejection under 35 U.S.C. § 102/103

Claims 1-17, 19 and 21-28 were rejected under 35 U.S.C. § 102 as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over, U.S. Patent No. 5,711,967 ("Juch"). The applicant respectfully traverse the rejection if the rejection is applied to the claims as amended.

Juch

Juch discloses formulations comprising the non-steroidal anti-inflammatory drug, diclofenac sodium. There is no requirement in Juch that the compositions described therein be adapted to deliver diclofenac specifically to the colonic region. The composition in Juch comprises "an outer film coating resistant to gastric juice" (col. 4, lines 22-23) which must satisfy the criteria laid down in USP XXII page 1580. Nonetheless, the equivalent passage from

USP XXIII (p. 1795) indicates an initial incubation period of 2 hours in 0.1 M hydrochloric acid after which the dissolution medium is changed to pH 6.8 buffer.

Figures 2-3 of Juch show the dissolution profiles of enteric coated pellets in an intestinal fluid. None of the pellets in either Figure 2 or Figure 3 have been subjected to the two hour 0.1 M hydrochloric acid incubation as recommended by USP XXII. Assuming that the "intestinal fluid" used for these dissolution tests was pH 6.8 buffer, as recommended by the USP for the enteric-coating test, then the dissolution profiles would not be expected to provide colon-targeted drug release. One of ordinary skill in the art will appreciate that a period of around 90 minutes at pH 6.8 during which no drug is released corresponds to achieving colon specific delivery of drug *in vivo*. As such, Figures 2-3 demonstrate that Juch fails to achieve colon specific delivery of diclofenac sodium. Therefore, Juch does not anticipates claims 1-17, 19 and 21-28.

Neither does Juch make obvious claims 1-17, 19, and 21-28. Diclofenac is a non-steroidal anti-inflammatory drug ("NSAID"). It is well known in the art that delivery of NSAIDs that they should be targeted to the small intestine, which has a large surface area, in order to provide an effective and rapid systemic delivery. Therefore, Juch not only fails to lead one of ordinary skill in the art to, but also teaches away from, the subject matter of claims 1-17, 19, and 21-28. Nor can Just lead one of ordinary skill in the art to have a reasonable expectation of the subject matter of claims 1-17, 19, and 21-28. As such, Juch does not make obvious claims 1-17, 19 and 21-22.

Allowance of claims 1-14 and 21-28 is therefore earnestly solicited. A copy of the claims as amended and a clean copy of the pending claims are attached in the appendices.

Respectfully submitted,

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I hereby certify that this paper, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Aisha Wyatt

Date: June 25, 2001

Appendix I. Pending claims upon entry of the amendments

1. (Once amended) A controlled release composition comprising pellets, wherein each pellet comprises an inner core comprising a drug which possesses

(a) a free acid group which can be converted into an alkali metal salt, and

(b) a pKa in the range 2.0 to 9.0,

wherein the inner core is coated with a rate-controlling membrane that determines drug release,

wherein the drug is present as a salt that displays higher solubility at pH 4.5 to 8.0 than the corresponding compound containing a free acid group, and

wherein the composition is adapted to prevent release of drug until the composition reaches the terminal ileum or the colon following oral administration of the composition.

2. (Once amended) The composition of claim 1 wherein the drug is a thromboxane synthase A_2 inhibitor or a thromboxane A_2/prostaglandin endoperoxide receptor antagonist.

3. (Once amended) The composition of claim 2 wherein the drug is ridogrel.

4. (Once amended) The composition of claim 1 wherein the rate-controlling membrane comprises a material which forms a water-insoluble, but water-permeable layer and from which release of the drug is by diffusion through the layer.

5. (Once amended) The composition of claim 4 wherein the rate-controlling membrane is formulated from a methacrylate copolymer or ethylcellulose.

6. (Once amended) The composition of claim 5 wherein the rate-controlling membrane is formulated from EUDRAGIT™ NE30D.

7. (Once amended) The composition of claim 5 wherein the rate-controlling membrane is ethylcellulose.

8. (Once amended) The composition of claim 1 wherein the inner core is a sugar sphere.

9. (Once amended) The composition of claim 1 wherein the salt is at least 10 times more soluble than the free acid form of the drug at pH 4.5 to 8.0 at 37 °C.

10. (Amended) The composition of claim 9 wherein the salt is at least 100 times more soluble than the free acid form of the drug.

11. (Once amended) The composition of claim 1 wherein the salt is an alkali metal salt.

12. (Once amended) The composition of claim 11 wherein the alkali metal is sodium or potassium.

13. (Twice amended) The composition of claim 1 wherein the pellets are administered in a starch capsule coated with a combination of polymethacrylates [that] which capsule is so designed to disintegrate and release the pellets in the terminal ileum or in the colon.

14. (Once amended) The composition of claim 1 wherein the drug is used for a treatment selected from the group consisting of ulcerative colitis, Crohn's disease, irritable bowel syndrome, and inflammatory bowel disease.

15. (Twice amended) A method for making a composition comprising pellets, wherein each pellet comprises an inner core comprising a drug which possesses

(a) a free acid group which can be converted into an alkali metal salt, and

(b) a pKa in the range 2.0 to 9.0,

wherein the inner core of the pellets is coated with a rate-controlling membrane that determines drug release, wherein the drug is present as a salt that displays higher solubility at pH 4.5 to 8.0 than the corresponding compound containing a free acid group, and

wherein the composition is adapted to prevent release of drug until the composition reaches the terminal ileum or the colon following oral administration of the composition, the method comprising

making a salt of the drug, [and]

coating the salt onto the inner cores, and

coating the rate-controlling membrane that determines drug release onto the salt.

16. (Twice amended) The method of claim 15 wherein the salt is made in a solution used in the coating of the inner cores.

17. (Once amended) A method of improving the controlled release profile of a drug with a rapidly changing solubility in the pH range 4.5 to 8.0, the method comprising

administering the drug in a composition comprising pellets,

wherein each pellet comprises an inner core comprising the drug which possesses

(a) a free acid group which can be converted into an alkali metal salt and

(b) a pKa in the range 2.0 to 9.0,

wherein the inner core is coated with a rate-controlling membrane that determines drug release, wherein the drug is present as a salt that displays higher solubility at pH 4.5 to 8.0 than the corresponding compound containing a free acid group, and wherein the composition is adapted to prevent release of drug until the composition reaches the terminal ileum or the colon following oral administration of the composition.

19. (Once amended) A method of treatment of ulcerative colitis, Crohn's disease, irritable bowel syndrome, and/or inflammatory bowel disease, the method comprising

administering to a patient in need of treatment a composition comprising pellets,

wherein each pellet comprises an inner core comprising a drug which possesses

(a) a free acid group which can be converted into an alkali metal salt, and

(b) a pKa in the range 2.0 to 9.0,

wherein the inner core is coated with a rate-controlling membrane that determines drug release, wherein the drug is present as a salt that displays higher solubility at pH 4.5 to 8.0 than the corresponding compound containing a free acid group, and wherein the composition is adapted to prevent release of drug until the composition reaches the terminal ileum or the colon following oral administration of the composition.

21. (Once amended) The composition of claim 1 wherein the pellets are compressed into tablets which are coated with a material to prevent release of drug until the composition reaches the terminal ileum or the colon following oral administration of the composition.

22. The composition of claim 1 wherein the core is between about 0.3 to 5 mm in size.

23. The method of claim 15 wherein the salt, after being made, is recovered in solid form before coating onto the inner cores.

24. The composition of claim 1 wherein the pellets are administered in a capsule coated with a mixture of a first copolymer of methacrylic acid and methylmethacrylate and a second copolymer of methacrylic acid and methylmethacrylate, which disintegrate and release the pellets in the terminal ileum or in the colon following oral administration.

25. The composition of claim 24 wherein the first copolymer dissolves at pH 6 or greater and comprises about 48% methacrylic acid units per gram dry weight of first copolymer and wherein the second copolymer dissolves at pH 7 or greater and comprises about 29% methacrylic acid units per gram dry weight of second copolymer.

26. The composition of claim 25 wherein the ratio of first polymer to second polymer in the mixture is between 100:0 and 20:80.

27. The composition of claim 25 wherein the capsule coating has a thickness between about 150 and 200 μm.

28. The composition of claim 25 wherein the capsule coating has a thickness between about 80 and 120 μm.

Appendix II. Clean copy of pending claims upon entry of the amendments

1. A controlled release composition comprising pellets, wherein each pellet comprises an inner core comprising a drug which possesses

(a) a free acid group which can be converted into an alkali metal salt, and

(b) a pKa in the range 2.0 to 9.0,

wherein the inner core is coated with a rate-controlling membrane that determines drug release,

wherein the drug is present as a salt that displays higher solubility at pH 4.5 to 8.0 than the corresponding compound containing a free acid group, and

wherein the composition is adapted to prevent release of drug until the composition reaches the terminal ileum or the colon following oral administration of the composition.

2. The composition of claim 1 wherein the drug is a thromboxane synthase A_2 inhibitor or a thromboxane A_2/prostaglandin endoperoxide receptor antagonist.

3. The composition of claim 2 wherein the drug is ridogrel.

4. The composition of claim 1 wherein the rate-controlling membrane comprises a material which forms a water-insoluble, but water-permeable layer and from which release of the drug is by diffusion through the layer.

5. The composition of claim 4 wherein the rate-controlling membrane is formulated from a methacrylate copolymer or ethylcellulose.

6. The composition of claim 5 wherein the rate-controlling membrane is formulated from EUDRAGIT™ NE30D.

7. The composition of claim 5 wherein the rate-controlling membrane is ethylcellulose.

8. The composition of claim 1 wherein the inner core is a sugar sphere.

9. The composition of claim 1 wherein the salt is at least 10 times more soluble than the free acid form of the drug at pH 4.5 to 8.0 at 37 °C.

10. The composition of claim 9 wherein the salt is at least 100 times more soluble than the free acid form of the drug.

11. The composition of claim 1 wherein the salt is an alkali metal salt.

12. The composition of claim 11 wherein the alkali metal is sodium or potassium.

13. The composition of claim 1 wherein the pellets are administered in a starch capsule coated with a combination of polymethacrylates which capsule is so designed to disintegrate and release the pellets in the terminal ileum or in the colon.

14. The composition of claim 1 wherein the drug is used for a treatment selected from the group consisting of ulcerative colitis, Crohn's disease, irritable bowel syndrome, and inflammatory bowel disease.

15. A method for making a composition comprising pellets,
wherein each pellet comprises an inner core comprising a drug which possesses
(a) a free acid group which can be converted into an alkali metal salt, and
(b) a pKa in the range 2.0 to 9.0,
wherein the inner core of the pellets is coated with a rate-controlling membrane that determines drug release, wherein the drug is present as a salt that displays higher solubility at pH 4.5 to 8.0 than the corresponding compound containing a free acid group, and
wherein the composition is adapted to prevent release of drug until the composition reaches the terminal ileum or the colon following oral administration of the composition, the method comprising
making a salt of the drug,
coating the salt onto the inner cores, and
coating the rate-controlling membrane that determines drug release onto the salt.

16. The method of claim 15 wherein the salt is made in a solution used in the coating of the inner cores.

17. A method of improving the controlled release profile of a drug with a rapidly changing solubility in the pH range 4.5 to 8.0, the method comprising

administering the drug in a composition comprising pellets,

wherein each pellet comprises an inner core comprising the drug which possesses

(a) a free acid group which can be converted into an alkali metal salt and

(b) a pKa in the range 2.0 to 9.0,

wherein the inner core is coated with a rate-controlling membrane that determines drug release, wherein the drug is present as a salt that displays higher solubility at pH 4.5 to 8.0 than the corresponding compound containing a free acid group, and wherein the composition is adapted to prevent release of drug until the composition reaches the terminal ileum or the colon following oral administration of the composition.

19. A method of treatment of ulcerative colitis, Crohn's disease, irritable bowel syndrome, and/or inflammatory bowel disease, the method comprising

administering to a patient in need of treatment a composition comprising pellets,

wherein each pellet comprises an inner core comprising a drug which possesses

(a) a free acid group which can be converted into an alkali metal salt, and

(b) a pKa in the range 2.0 to 9.0,

wherein the inner core is coated with a rate-controlling membrane that determines drug release, wherein the drug is present as a salt that displays higher solubility at pH 4.5 to 8.0 than the corresponding compound containing a free acid group, and wherein the composition is adapted to prevent release of drug until the composition reaches the terminal ileum or the colon following oral administration of the composition.

C3

21. The composition of claim 1 wherein the pellets are compressed into tablets which are coated with a material to prevent release of drug until the composition reaches the terminal ileum or the colon following oral administration of the composition.

22. The composition of claim 1 wherein the core is between about 0.3 to 5 mm in size.

23. The method of claim 15 wherein the salt, after being made, is recovered in solid form before coating onto the inner cores.

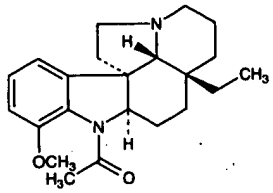
24. The composition of claim 1 wherein the pellets are administered in a capsule coated with a mixture of a first copolymer of methacrylic acid and methylmethacrylate and a second copolymer of methacrylic acid and methylmethacrylate, which disintegrate and release the pellets in the terminal ileum or in the colon following oral administration.

25. The composition of claim 24 wherein the first copolymer dissolves at pH 6 or greater and comprises about 48% methacrylic acid units per gram dry weight of first copolymer and wherein the second copolymer dissolves at pH 7 or greater and comprises about 29% methacrylic acid units per gram dry weight of second copolymer.

26. The composition of claim 25 wherein the ratio of first polymer to second polymer in the mixture is between 100:0 and 20:80.

27. The composition of claim 25 wherein the capsule coating has a thickness between about 150 and 200 μm.

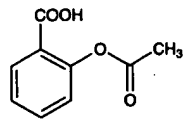
28. The composition of claim 25 wherein the capsule coating has a thickness between about 80 and 120 μm.



Needles or prisms from alc, needles from petr ether. mp 208°. Sublimes 180°. bp_2 220°. $[\alpha]_D^{15}$ −100.2° (alc); $[\alpha]_D$ −93° (chloroform). uv max (methanol): 218, 255, 280-290 nm (log ε 4.52, 4.04, 3.53-3.40). One gram dissolves in 60 ml water, 50 ml alc, 100 ml ether. Also sol in benzene, chloroform, petr ether. LD_{50} in mice: 40 mg/kg i.p., *RTECS* **Vol. 1,** R. J. Lewis, R. L. Tatken, Eds. (1979) p 156.

N-Formyl-*N*-deacetylaspidospermine, $C_{21}H_{28}N_2O_2$, *vallesine.* Structure: Taylor *et al., Helv. Chim. Acta* **42,** 2750 (1959). Long, fine needles from acetone, mp 154-156°. $[\alpha]_D^{24}$ −91 ± 2° (c = 1.814 in abs alc). uv max: 211, 250 nm (log ε 4.47, 3.94).

886. Aspirin. *2-(Acetyloxy)benzoic acid; salicylic acid acetate;* 2-acetoxybenzoic acid; acetylsalicylic acid; Acenterine; Aceticyl; Acetophen; Acetosal; Acetosalic Acid; Acetosalin; Acetylin; Acetyl-SAL; Acimetten; Acylpyrin; Arthrisin; A.S.A.; Asatard; Aspro; Asteric; Caprin; Claradin; Colfarit; Contrheuma retard; Duramax; ECM; Ecotrin; Empirin; Encaprin; Endydol; Entrophen; Enterosarine; Helicon; Levius; Longasa; Measurin; Neuronika; Platet; Rhodine; Salacetin; Salcetogen; Saletin; Solprin; Solpyron; Xaxa. $C_9H_8O_4$; mol wt 180.16. C 60.00%, H 4.48%, O 35.52%. Prepn: C. Gerhardt, *Ann.* **87,** 149 (1853). Manuf from salicylic acid and acetic anhydride: Faith, Keyes & Clark's *Industrial Chemicals,* F. A. Lowenheim, M. K. Moran, Eds. (Wiley-Interscience, New York, 4th ed., 1975) pp 117-120. Crystallization from acetone: Hamer, Phillips, U.S. pat. **2,890,240** (1959 to Monsanto). Novel process involving distillation: Edmunds, U.S. pat. **3,235,583** (1966 to Norwich Pharm.). Crystal structure: P. J. Wheatley, *J. Chem. Soc. (Suppl.)* **1964,** 6036. Toxicity data: E. R. Hart, *J. Pharmacol. Exp. Ther.* **89,** 205 (1947). Evaluation as a risk factor in Reye's syndrome: P. J. Waldman *et al., J. Am. Med. Assoc.* **247,** 3089 (1982). Review of clinical trials in prevention of myocardial infarction and stroke: P. C. Elwood, *Drugs* **28,** 1-5 (1984). Symposium on aspirin therapy: *Am. J. Med.* **74,** no. 6A, 1-109 (1983). Comprehensive description: K. Florey, *Anal. Profiles Drug Subs.* **8** 1-46 (1979). Monograph: M. J. H. Smith, P. K. Smith, *The Salicylates* (Interscience, New York, 1966) 313 pp. Book: *Acetylsalicylic Acid,* H. J. M. Barnett *et al.,* Eds. (Raven, New York, 1982) 278 pp.



Monoclinic tablets or needle-like crystals. d 1.40. mp 135° (rapid heating); the melt solidifies at 118°. uv max (0.1*N* H_2SO_4): 229 nm ($E_{1cm}^{1\%}$ 484); ($CHCl_3$): 277 nm ($E_{1cm}^{1\%}$ 68). Is odorless, but in moist air it is gradually hydrolyzed into salicylic and acetic acids and acquires the odor of acetic acid. Stable in dry air. pK (25°) 3.49. One gram dissolves in 300 ml water at 25°, in 100 ml water at 37°, in 5 ml alcohol, 17 ml chloroform, 10-15 ml ether. Less soluble in anhydr ether. Decomp by boiling water or when dissolved in solns of alkali hydroxides and carbonates. LD_{50} orally in mice, rats: 1.1, 1.5 g/kg (Hart).

Guaiacol ester, $C_{16}H_{14}O_5$, *guacetisal, Broncaspin, Guaiaspir.*

Methyl ester, *see* Methyl Acetylsalicylate.

Phenyl ester, *see* Phenyl Acetylsalicylate.

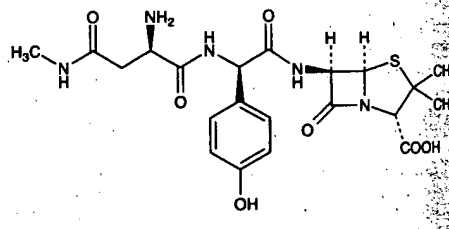
Inorganic salts of acetylsalicylic acid are soluble in water (esp the Ca salt, *q.v.*), but are decomposed quickly.

Pharmaceutical Incompat. (from *Remington's Pharmaceutical Sciences):* Aspirin forms a damp to pasty mass when triturated with acetanilide, phenacetin, antipyrine, aminopyrine, methenamine, phenol or phenyl salicylate. Powders containing aspirin with an alkali salt such as sodium bicarbonate become gummy on contact with atmospheric moisture. Hydrolysis occurs in admixture with salts contg water of crystallization. Solns of the alkaline acetates and citrates, as well as alkalies themselves, dissolve aspirin but the resulting solns hydrolyze rapidly to form salts of acetic and salicylic acids. Sugar and glycerol have been shown to hinder this decompn. Aspirin very slowly liberates hydriodic acid from potassium or sodium iodide. Subsequent oxidation by air produces free iodine.

THERAP CAT: Analgesic; antipyretic; anti-inflammatory.

THERAP CAT (VET): Analgesic; antipyretic; anti-inflammatory; anticoagulant.

887. Aspoxicillin. *[2S-(2α,5α,6β)]-N-Methyl-D-asparaginyl-N-(2-carboxy-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-6-yl)-D-2-(4-hydroxyphenyl)glycinamide;* 6-[D-2-(D-2-amino-3-*N*-methylcarbamoylpropionamido)-2-*p*-hydroxyphenylacetamido]penicillanic acid; (2*S*,5*R*,6*R*)-6-[(2*R*)-2-[(2*R*)-2-amino-3-(methylcarbamoyl)propionamido]-2-(4-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid; N^4-methyl-D-asparaginylamoxicillin; ASPC; TA-058; Doyle. $C_{21}H_{27}N_5O_8S$; mol wt 493.54. C 51.11%, H 5.51%, N 14.19%, O 22.69%, S 6.50%. Semisynthetic penicillin. Prepn: M. Kawazu *et al.,* Ger. pat. **2,638,067;** *eidem,* U.S. pat. **4,053,609** (both 1977 to Tanabe); prepn and antibacterial activity: M. Wagasuma *et al., J. Antibiot.* **36,** 147 (1985). Mechanism of action study: T. Nishino *et al., Chemotherapy (Tokyo)* **33,** 112 (1985), *C.A.* **103,** 34792v (1985). Toxicological study: M. Takeshita *et al., Oyo Yakuri* **30,** 687 (1985), *C.A.* **104,** 101990u (1986). HPLC determn in serum: J. Knöller *et al., Zentralblatt Bakteriol. Mikrobiol. Hyg.* **265,** 176 (1987). Clinical evaluation in ocular infections: M. Ooishi *et al., Acta Med. Biol.* **34,** 1 (1986). Series of articles on antibacterial activity, pharmacology and clinical efficacy: *Chemotherapy (Tokyo)* **32,** Suppl. 2, 1-791 (1984).



Colorless crystalline powder, mp 195-198° (dec).

THERAP CAT: Antibacterial.

888. Astacin. *β,β-Carotene-3,3',4,4'-tetrone;* 3,4,3',4'-tetraketo-β-carotene; 3,3'-dihydroxy-2,3,2',3'-tetradehydro-β,β-carotene-4,4'-dione; astacene. $C_{40}H_{48}O_4$; mol wt 592.82. C 81.04%, H 8.16%, O 10.80%. Red carotenoid pigment isolated from biological material originating from crustacea, algae, sponges, protozoa, fish and reptiles. Small amounts were isolated from the fat of mammals (whales, *Balaenoptera musculus).* Occurs together with astaxanthin from which it is formed by autoxidation. Appears to be an artifact rather than a natural product. Isoln from lobster shells: Kuhn, Lederer, *Ber.* **66,** 488 (1933). Structure: Karrer *et al., Helv. Chim. Acta* **17,** 412, 745 (1934); **18,** 99 (1935); **19,** 479 (1936). Total synthesis: J. B. Davis, B. C. L. Weedon, *Proc. Chem. Soc.* **1960,** 182; E. Widmer *et al., Helv. Chim. Acta* **65,** 671 (1982). Prepn by autoxidation of canthaxanthin: R. D. G. Cooper *et al., J. Chem. Soc. Perkin Trans. I* **1975,** 2195.